

Material–tissue Interfaces: The Role of Surface Properties and Processes

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The introduction of a foreign material into living tissue—intentionally as in biomedical applications (implants, prostheses, drugs) or unintentionally as when minerals or fibers are inhaled—results in the creation of interfaces between the material and the surrounding tissue. This article identifies and discusses the possible role of material surface properties and molecular processes occurring at such interfaces. For kinetic and thermodynamic reasons, surfaces are different from the corresponding bulk of the material, and contain reactive (unsaturated) bonds, which in turn lead to the formation of surface reactive layers (e.g., surface oxides on metals) and adsorbed contamination layers. The encounter with the biological environment leads to further surface reactions modifying the surface, and to the adsorption of water, ions, and biomolecules, which are continuously exchanged. The exact nature of the dynamic, adsorbed water, ions, and biomolecule coating in turn influences the behavior of cells approaching the material surface, and hence the tissue response. — *Environ Health Perspect* 102(Suppl 5):41–45 (1994)

Key words: surface, interface, metal oxide, biomolecules, water, ions, cell membrane, biomaterials

Introduction

Imagine that a cavity were created in bone, soft tissue, or blood without initially perturbing the remaining tissue. If the cavity were filled with a foreign material, an interface would have been created between the native tissue and the foreign material (Figure 1). The tissue consists of a variety of molecules—water, oxygen, negative and positive ions, proteins, and other biomolecules, which may be built up into larger structures such as cells and cell membranes. The foreign material could consist of individual atoms, molecules, or larger polymeric structures. These biological and nonbiological structures meet and interact at the interface. This article discusses some of the events likely to occur at the interface, in particular how they are influenced by, and connected to, the surface properties of the foreign material.

The Material Surface

The surface of a material is a termination of an extended, three-dimensional structure, and thus generally represents an increase in energy, the surface energy. On

the atomic scale this energy is present as unterminated (unsaturated or “dangling”) bonds. If there is a reactive environment such as air or water at a metal surface, the bonds react in much less than a second to form new bonds and compounds, thus lowering the surface energy. Therefore, a material surface usually has a different chemical composition from its bulk, as for example the oxide overlayers on almost all metals.

Hydroxylated ceramic surfaces provide a second example. Even macroscopically inert surfaces such as gold or diamond have a tendency to lower their surface energy by suitable terminations on the atomic scale. For example, diamond may terminate by C—H bonds at the surface.

If a surface thus stabilized is placed in a new environment, it is likely to react again to lower further the energy of the system. There is thus a built-in thermodynamic driving force for reactions of various kinds at tissue–material interfaces. Only in two exceptional cases do no reactions occur: either when the separated material and tissue systems have the lowest thermodynamic state, or when kinetic barriers prevent all possible reactions (1–3).

Titanium, which is used for dental implants (4) and in orthopedic devices (5,6) provides a specific example. When fresh titanium is exposed to air it reacts rapidly with atmospheric oxygen to form a surface oxide which is typically a few nanometers thick. The composition and thickness of this oxide layer have been extensively analyzed (7–15), for a variety of treatment conditions. The oxide stoichiometry is approximately TiO_2

(7,14,15). For oxidation temperatures $<200^\circ\text{C}$, the oxide appears amorphous and glass-like, while thicker oxides formed at elevated temperatures or by electrochemical oxidation are more crystalline (8,10,11).

The surface is never perfectly clean TiO_2 , for the TiO_2 -terminated surface tends to bind molecules or atoms from the surroundings as a monomolecular layer. Typically it picks up hydrocarbons present as low-level impurities in the ambient air (8,16). Figure 2 shows spectra that represent the chemical composition of the outermost atomic layers recorded by X-ray photoemission spectroscopy (XPS or ESCA) of different titanium surfaces. Combining the information from these spectra with other similar information, and with measurements of oxide thickness, etc., gives a fairly realistic picture of a real surface meeting the tissue environment (Figure 3).

Processes at the Material–tissue Interface

The chemical constituents and pH, for example, of the biological environment

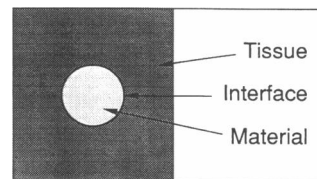


Figure 1. The implantation of a foreign material in any tissue will create an interface between the material and the biological system.

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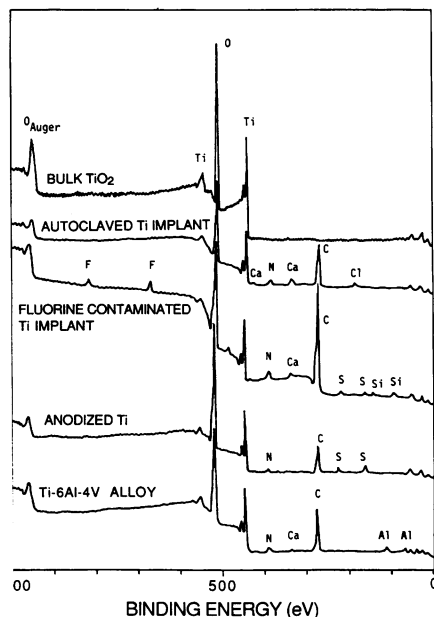


Figure 2. XPS spectra from differently prepared Ti surfaces. All spectra are dominated by Ti and O signals due to the surface oxide (TiO_2). In most cases, a strong C signal from hydrocarbons adsorbed from the ambient air is also detected, as well as minor amounts of impurities originating from differences in the preparation of the surfaces.

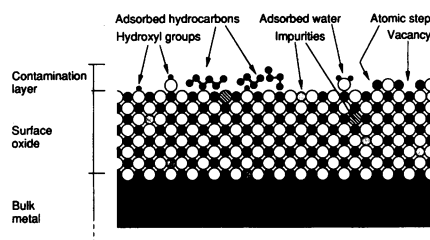


Figure 3. Schematic illustration of a "real" metal surface depicting the surface oxide with minor impurities, including surface hydroxyl groups and water, and the adsorbed contamination layer. Structural defects (steps and vacancies) are also indicated.

influence the interaction at the surface (1,3,17) (Figure 4). If the material is a metal, degradation by corrosion may result in release of metal ions from the oxidized metal surface into solution, which may then migrate throughout the biological system, potentially producing negative systemic effects such as allergic reactions. This has been demonstrated in animal experiments (18), and in humans (19), with metal ions such as Ni, Cr, Al, and V.

Even if dissolution of ions does not occur, the surface may be attacked by the tissue by an oxidative process if the oxide layer, instead of remaining passive, becomes thicker via anion or cation transport through the oxide layer. This can

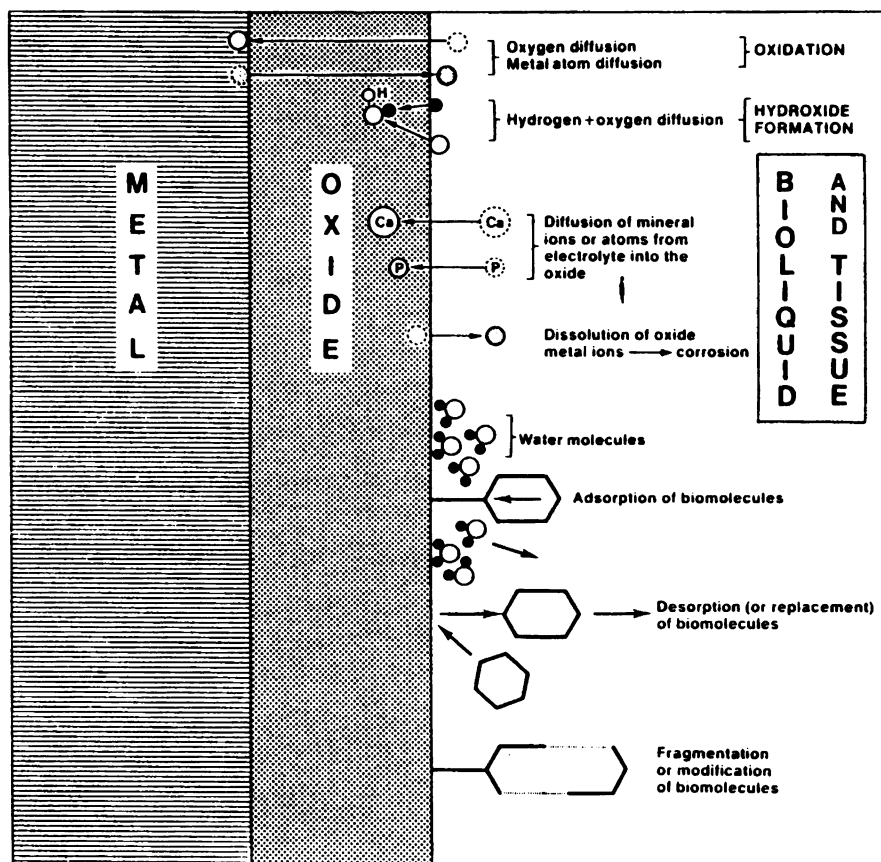


Figure 4. Schematic illustration of some molecular processes at the interface between a material and the surrounding biological environment. The top half of the figure shows processes that modify the material; the lower half shows interactions between the surface and biomolecules.

occur in the presence of oxygen radicals and peroxy species, or certain complex-forming ions in the biological environment (20,21), or catalyzing species that accelerate oxidation. If oxide growth occurs *in vivo*, as has been demonstrated experimentally (22,23), it may be accompanied by inclusion of ions present in the bioliquid (as indicated for Ca and P in Figure 4). Thus, the surface of the material, and its interface with the tissue, may be very dynamic and may undergo continuous remodeling. Biodegradable materials constitute an extreme and intentional case of this event—the whole material eventually is dissolved. In the other extreme, like bone anchored devices, the requirement is a stable, yet fully tissue-integrated device, which may require an initial or continuous microscopic remodeling of the surface, but at a rate that has a negligible effect on the macroscopic dimensions of the implant (Figure 5).

The material surface is, in relation to the tissue, a foreign chemical species that has reactive sites, such as unsaturated chem-

ical bonds, which can either be the main constituents of the surface or impurities that have become incorporated in it. The termination of polymer chains on polymer surfaces also may be reaction sites, which can interact with reactive groups, for example, on protein and carbohydrate molecules.

Reactions between a biomolecule and the material surface may lead to a permanent or temporary bond formation, which are either weak (1), of van der Waals or hydrogen bonding type, or stronger ionic or covalent bonds (1). In contrast, interactions may be so strong that, for example, proteins are reversibly or irreversibly denatured by formation of multiple bonds with the surface, accompanied by breaking of internal bonds within the protein (24–26). Such interaction might lead to total dissociation of the biomolecules, as is frequently seen with smaller molecules like O_2 , H_2 , H_2O , and hydrocarbons on metal and oxide surfaces (27). It also may lead to catalytic action that irreversibly modifies the protein conformation and composition,

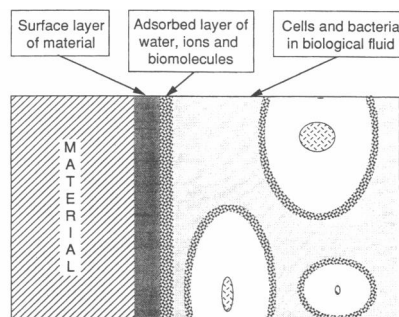


Figure 5. Schematic picture of cells close to the material surface, illustrating that the cells interact with the dynamic hydration (water and ions) and protein layers, which cover the material surface in the biological environment.

even if it is eventually released from the surface.

The molecular events at the material-tissue interface involve small molecules, like water, which can dissociate to OH-groups or bind to the surface by hydrogen bonds. They also involve larger molecules like proteins, which sometimes denature (Figure 6). This hydration and protein layer is dynamic and surface specific since different surfaces will develop very different coatings in the same tissue, because of their different chemical properties.

Eventually the larger structures like cells, which have lower mobility, will reach the surface with its organic overlayer (Figure 6). Since both the cell membrane with its coating of biomolecules and the material surface are dynamic, they can exchange proteins, ions, and other substances, and form a complex and dynamic interface. Depending on the nature of the material surface and its organic coating, cells react differently to different biomaterials. They may experience the surface as a serious perturbation and react violently inducing an inflammatory response; if the surface is experienced as "tissue-like," no reactions or only mild ones may occur.

The connection between microscopic events and properties at the atomic and molecular levels at the tissue-material interface and the macroscopic events and structures are depicted in Figure 5. The surface-specific reactions form a dynamic surface coating of molecular dimensions, which eventually interacts with the cells and their sensors, which in turn react in different ways depending on the exact nature of the original surface. Figure 7 schematically outlines a time-space scenario along these lines for the case of a bone-anchored implant.

Surface Characterization and Preparation

Surface characterization and controlled surface preparation, both on the atomic scale, are vital ingredients in any research effort to improve our understanding of the material-tissue interface and the processes occurring there. It is possible to analyze the outermost atomic layer(s) of a material with a sensitivity of down to 0.1 to 1% of a monolayer; the composition of the surface can be prepared with a similar degree of control. This constitutes an invaluable base for systematic studies of the material-tissue interface.

Research Needs and Opportunities

Although the ideas and suggestions developed below are intended to be applicable to implantable medical devices, they could apply to any type of material-tissue interactions.

The biomaterial-tissue interface is, as a research field, still in its infancy; and because little factual knowledge exists, much effort goes into formulating the central problems and questions and into developing better research methods. The need for knowledge from many different disciplines, which usually do not communicate with each other, is an obvious problem. Some key questions for the ongoing and future research are (3):

- Which biomolecules are adsorbed in the first monomolecular layer on the biomaterial surface?
- What type of bonding keeps the biomolecules to that surface? How strong are the bonds? Which part(s) of the adsorbed biomolecules is (are) involved in the bonding?
- Is the conformation of these biomolecules changed and if so, is the conformational change reversible or irreversible?
- Which molecules are bound in the second and third layer, etc., and how are they bound to each other?
- Is there a continuous exchange, over time, of the molecules adsorbed at the surface, and what are the time scales for such exchange?
- How close to the surface can cells come? Is there always a layer of extracellular components that separate cells from the surface?
- How does the surface influence cell differentiation and activity?
- How is information communicated between cells and biomaterial surfaces *in vivo*?
- How are water and hydrated ions structured at the interface and how do they bind to the surface? How does water bonding influence protein bonding, etc.?

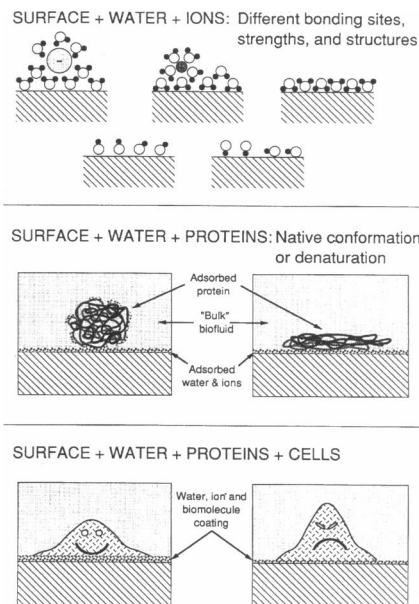


Figure 6. Schematic illustration of the material-tissue interaction at different levels. The original surface properties of the material will eventually influence the behavior of the cells and the macroscopic development of the tissue, via interaction with water, ions, and biomolecules such as protein molecules.

- How does the chemical composition of the surface influence the biological response? What is the role of surface contamination?
- How important is the microstructure and topography of the surface?

It is evident that the implantation of a biomaterial device results in a series of coupled events, starting with the initial preparation of the implant. The surface properties of the implant may influence the later interface evolution as a "memory effect" by determining the nature of the water layer, which in turn determines the protein-surface and cell surface interactions. These interactions eventually determine the ultimate success or failure of the implant.

A research program addressing these issues will involve adsorption studies of water and proteins with kinetic methods, with a variety of spectroscopic methods of atomic resolution, microscopic methods to obtain the bonding, orientation, and structure of water and proteins on the surface, etc. Simplified model systems of simple molecules and well characterized surfaces as well as complex mixtures of biomolecules and heterogeneous surfaces will be employed. Cell level interaction studies are necessary, as well as real *in vivo* experiments. Some studies will concentrate on static situations (snap shot pictures); others

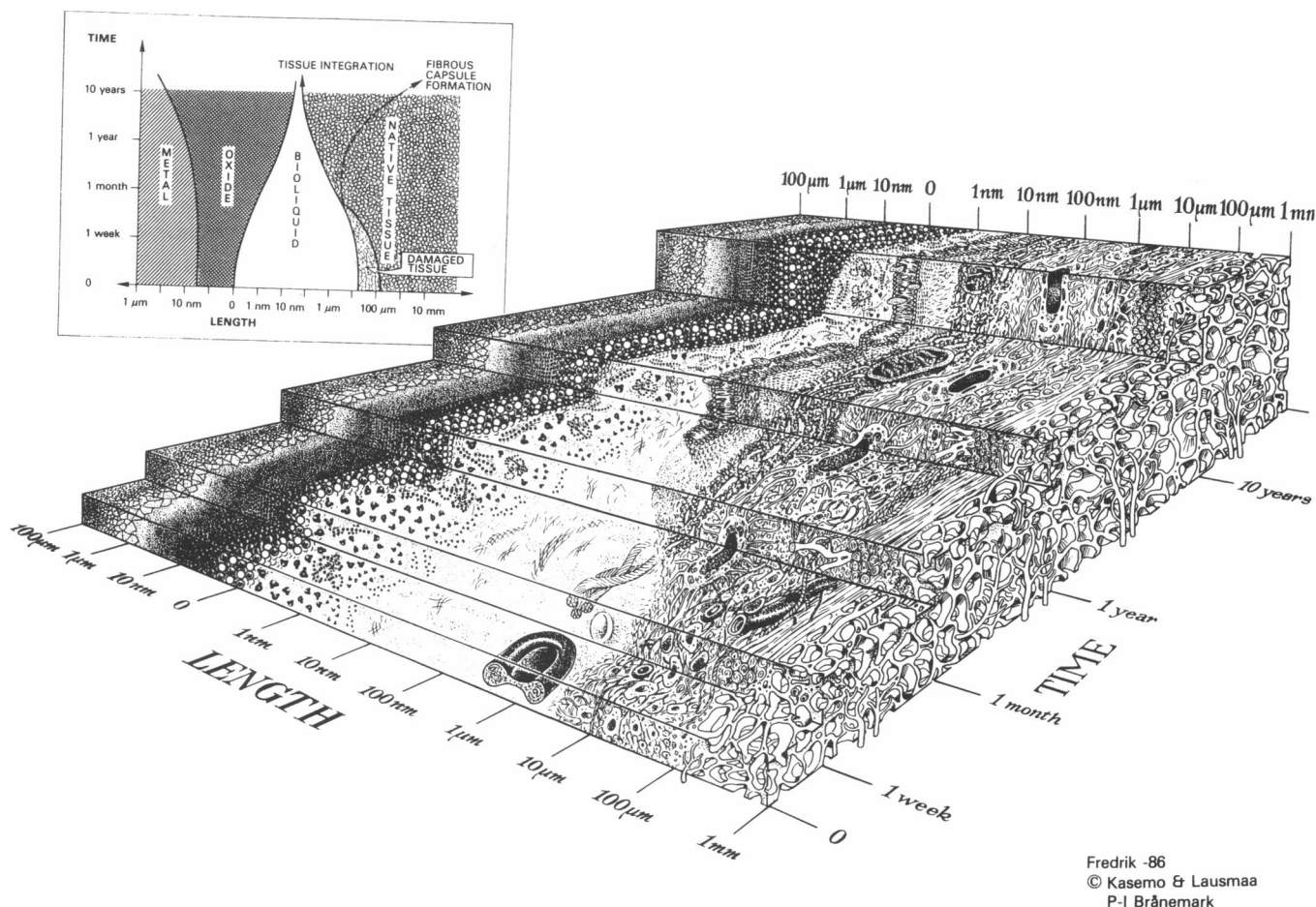


Figure 7. An artist's attempt to capture some of the complexity involved in the interaction between a material and living tissue, exemplified here by a titanium implant in bone. Note the wide range of dimensions and time scales that are relevant.

will attack the more difficult time evolution outlined in Figure 7. There will be a demand for new and improved experimental methods.

The scenario outlined above could equally well have started from the highest complexity, the *in vivo* situation, then approached the molecular level situation in descending order of complexity and length

scales. The mutual interaction between research efforts at all these levels of complexity and size eventually will allow us to draw a real, rather than hypothetical, interface scenario like the one in Figure 7.

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